

[PDF OF THIS ARTICLE](#)See Related:
[Authors' Articles](#)[Return to
Table of Contents](#)[ABSTRACT](#)[INTRODUCTION](#)[METHODS](#)[RESULTS](#)[COMMENT](#)[AUTHOR/ARTICLE
INFORMATION](#)[REFERENCES](#)[INDEX OF
FIGURES AND
TABLES](#)

HIV Infection in Women in the United States

Status at the Millennium

By **Shannon L. Hader, MD, MPH; Dawn K. Smith, MD, MPH, MS; Janet S. Moore, PhD; Scott D. Holmberg, MD, MPH**

Context During the past decade, knowledge of human immunodeficiency virus (HIV) infection in women has expanded considerably but may not be easily accessible for use in understanding and prioritizing the clinical needs of HIV-infected women.

Objectives To perform a comprehensive review of epidemiologic, clinical, psychosocial, and behavioral information about HIV in women, and to recommend an agenda for future activities.

Data Sources A computerized search, using MEDLINE and AIDSline, of published literature was conducted; journal articles from January 1981 through July 2000 and scientific conference presentations from January 1999 through July 2000 were retrieved and reviewed for content; article reference lists were used to identify additional articles and presentations of interest.

Study Selection Data from surveillance and prospective cohort studies with at least 20 HIV-infected women and appropriate comparison groups were preferentially included.

Data Extraction Included studies of historical importance and subsequent refined analyses of topics covered therein; these and studies with more current data were given preference. Four studies involving fewer than 20 women were included; 2 studies were of men only.

Data Synthesis Women account for an increasing percentage of all acquired immunodeficiency syndrome (AIDS) cases, from 6.7% (1819/27 140 cases) in 1986 to 18% (119 810/724 656 cases) in 1999. By the end of 1998, of all newly reported AIDS cases among women, proportionally more were in the South (41%), among black women (61%), and from heterosexual transmission (38%). Of note, increasingly more women have no identified or reported risk, about half or more of whom are estimated to be infected heterosexually. It is estimated that a total of at least 54% of women newly reported with AIDS in 1998 acquired HIV through heterosexual sex, including women in the no identified or reported risk category estimated to have been infected heterosexually, meeting the surveillance heterosexual risk definition. Natural history, progression, survival, and HIV-associated illnesses—except for those of the reproductive tract—thus far appear to be similar in HIV-infected women and men. Although antiretroviral therapy has proven to be highly effective in improving HIV-related morbidity and mortality rates, women may be less likely than men to use these therapies. Drug use, high-risk sex behaviors, depression, and unmet social needs interfere with women's use of available HIV prevention and treatment resources.

Conclusions Continued research on HIV pathogenesis and treatment is needed; however, emphasis should also be placed on using existing knowledge to improve the clinical care of women by enhancing use of available services and including greater use of antiretroviral therapy options, treating depression and drug use, facilitating educational efforts, and providing social support for HIV-infected women.

ABSTRACT

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INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

INDEX OF FIGURES AND TABLES

▼

Acquired immunodeficiency syndrome (AIDS), first reported in women in 1981,¹ had become the sixth leading cause of death in 25- to 44-year-old women in the United States by 1990.² Many unanswered questions arose about the natural history and progression of human immunodeficiency virus (HIV) disease in women,^{2,3} the survival of HIV-infected women,³ the appropriateness of AIDS case definitions for them,⁴ and the burden and manifestations of HIV-associated illnesses,⁴ particularly for sex-specific diseases.

To help answer these questions, epidemiologic studies were stratified by sex more frequently, clinical trials enrolled more women, and prospective studies were developed to focus on specific diseases in HIV-infected women. Also, 2 large prospective cohort studies of HIV-infected women and women at risk for HIV in the United States were created to examine a comprehensive set of questions: the Human Immunodeficiency Virus Research Study (HERS), started in 1991,⁵ and the Women's Interagency HIV Study (WIHS), started in 1994.⁶

In the United States, HIV infection remains a substantial problem for women. In 1998, AIDS was the fifth leading cause of death for women aged 25 to 44 years, and the third leading cause of death for black women in this age group.⁷ However, the past decade of research has led to a considerable expansion of knowledge regarding HIV infection in women. Because the results of research have been presented in a variety of settings, such as at conferences, in specialty journals, and within articles addressing issues not specific to HIV-infected women, this body of knowledge is not always easily accessible to clinicians or persons living with HIV/AIDS. Thus, we performed a comprehensive review of clinical literature relevant to HIV infection in women in the United States to enhance accessibility of this information so that it could be more readily used to improve the care of HIV-infected women. Literature on maternal-child HIV transmission has been recently reviewed in detail elsewhere^{8,9} and will not be extensively addressed herein.

METHODS

A computerized search of the published literature in MEDLINE and AIDSline was conducted using the keywords *women, HIV, AIDS, United States, HERS, WIHS, survival, disease progression, opportunistic infections, antiretroviral therapy, health care utilization, depression, violence, substance abuse, sexual behavior, and social problems*. Journal articles published from January 1981 through July 2000 were retrieved and reviewed for content, and their references were used to identify additional articles of interest. In addition, abstract books from recent (January 1999-July 2000) scientific conferences (Conferences on Retroviruses and

ABSTRACT

INTRODUCTION

METHODS
RESULTS
COMMENT
AUTHOR/ARTICLE INFORMATION
REFERENCES

INDEX OF FIGURES AND TABLES

Opportunistic Infections, Infectious Diseases Society of America, International AIDS Conference, the Interscience Conference on Antimicrobial Agents and Chemotherapy, and the National Conference on Women and HIV/AIDS) were reviewed. Data from surveillance studies and prospective cohort studies with at least 20 HIV-infected women and appropriate comparison groups were preferentially included. Studies of historical importance and subsequent refined analyses of topics covered therein, and studies with more current data were given preference. Four studies involving fewer than 20 women were included as were 2 studies of men only.

RESULTS

Changing Epidemiology

Women increasingly shoulder the burden of HIV disease. The cumulative percentage of all female AIDS cases increased from 6.7% (1819/27 140 cases) in 1986¹⁰ to 18% (119 810/724 656 cases) in 1999.¹¹ By 1999, women accounted for 23% of new AIDS diagnoses (10 780/46 137 cases) and 32% of newly reported HIV diagnoses (6855/21 186 cases).¹¹ The overall AIDS rates remain lower in women than in men, at 9.3 per 100 000 women compared with 32.4 per 100 000 men in 1999.¹¹

The surveillance data underscore an epidemiologic shift of an increasing proportion of AIDS cases occurring in women in the South (41%), in women with heterosexual risk (38%), and in black women (61%) (Figure 1). While the HIV epidemic is also increasingly affecting men in the South and black men,¹¹ the overall trends for women are distinct. The HIV epidemic in women initially centered on injection drug-using women in the urban Northeast,¹⁰ but now centers on women with heterosexual risk in the South,¹¹ traditionally a region with some of the highest sexually transmitted disease rates in the country. AIDS trends in Texas and Florida, which report almost half of the AIDS cases in the South, are similar to those for the South overall.¹¹ Women in rural areas are increasingly affected. For example, rural counties in Alabama have the highest AIDS incidence in the state, with women infected primarily through heterosexual sex.¹⁵

ABSTRACT
INTRODUCTION
METHODS
RESULTS
COMMENT
AUTHOR/ARTICLE INFORMATION
REFERENCES

In fact, by 1995, heterosexual transmission surpassed injection drug use (needle sharing) as the most common mode of transmission in all women (Figure 1).¹⁶ Increasingly, more women have no identified or reported risk,¹¹ approximately half or more of whom are estimated to be infected heterosexually, and an additional unknown number may be infected through heterosexual contact with a person not known to be infected or of high risk.¹² This may lead to more widespread heterosexual transmission if women do not recognize their risk.¹⁷ Using assumptions derived from a multisite validation study of AIDS cases reported from 1992 through 1995,¹² and data from the AIDS Public Information Data Set¹³ and HIV/AIDS Surveillance Reports,¹⁴ one can estimate that at least 54% of women newly reported with AIDS in 1998 acquired HIV through heterosexual sex. This estimate does not include women who were infected through heterosexual contact with a person not known to be infected or of high risk (the surveillance heterosexual risk definition).

INDEX OF

Black and Hispanic women have been disproportionately affected

**FIGURES AND
TABLES**

by HIV (Figure 1).¹¹ and now account for almost three quarters of HIV infections reported among women between the ages of 13 and 24 years.¹¹ Black women are more likely than white women to have acquired HIV heterosexually or with no identified or reported risk.^{11, 17}

Importantly, younger women are disproportionately at risk, reflected by estimates that 26% to 50% of all persons who acquire HIV heterosexually do so when they are teenagers or in their early 20s.¹⁷ Young women are at risk for infection at an earlier age than are heterosexual men, likely due to infection by older sex partners.¹⁸ Thus, women should receive effective and sustained prevention services starting at young ages.

Survival and Disease Progression

Survival and disease progression rates appear to be similar in HIV-infected women and men, with initially observed differences¹⁹ largely explained by differences in stage of disease, access to care and treatment, and initiation of timely therapy.^{20, 21} Further, despite initial concerns, pregnancy does not seem to markedly influence the course of HIV infection.²²

Biological markers are increasingly used to evaluate progression and guide therapeutic decisions. The CD4 cell count and plasma HIV RNA level (viral load) markers were originally explored in cohorts of men.²³ Sex differences in these markers have since become apparent,²⁴⁻²⁸ but have unclear clinical significance.^{20, 28, 29} Additional data on the significance of the differences in markers and implications for disease course are needed.

Women not infected with HIV have higher normal CD4 cell counts than men not infected with HIV.²⁴ Women infected with HIV maintain slightly higher CD4 cell counts than men with HIV through much of the course of infection.²⁵ While such differences appropriately engender the question of whether higher CD4 cell counts in women would potentially cause a delay in the initiation of antiretroviral therapy using current treatment guidelines,²⁵ women seem to demonstrate similar progression and survival at given CD4 cell counts.²⁰ Therefore, at this time, evidence does not strongly indicate a need to interpret CD4 cell counts differently based on sex.²⁹

Women also have lower HIV RNA levels than men with the same CD4 cell counts, especially early in infection.²⁶⁻²⁸ The HIV RNA levels seem to equalize as infection progresses, especially at CD4 cell counts of less than $200 \times 10^6/L$.³⁰ Variation in HIV RNA levels has been associated with hormonal changes during the ovulatory cycle.³¹ Although 1 study²⁶ estimated a 1.6-fold increased risk for progression for women at a given viral load, others have indicated no differences in rate of progression or death.²⁸ Thus, guidelines to date have not recommended sex-specific thresholds for initiation of antiretroviral treatment.^{29, 32} The need for knowledge of HIV pathogenesis, given its relevance to assessment of disease progression and related treatment strategies, makes additional research important in this area.

Illness Associated With HIV

In general, rates of HIV-associated illnesses are similar in women and men, with *Pneumocystis carinii* pneumonia, esophageal candidiasis, mycobacterial infections, bacterial pneumonias, and non-Hodgkin lymphomas being common manifestations of

ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

**AUTHOR/ARTICLE
INFORMATION**

REFERENCES

**INDEX OF
FIGURES AND
TABLES**

immunosuppression and appearing roughly equal in both sexes.³³ Women derive similar benefit from standard prophylaxis against and treatment for opportunistic infections.³⁵ Likewise, when stratified by HIV risk group, injection drug-using women have constitutional signs and symptoms similar to those of injection drug-using men.³⁶ Differences in symptoms between women with drug-use risk vs heterosexual risk seem due to the effects of injection drug use rather than HIV.²⁷

Sex-specific manifestations of HIV infection—specifically, gynecologic infections and malignancies—became apparent early in the epidemic,³⁷ and the AIDS case definition was modified in 1993 to include cervical cancer as an AIDS-defining condition.³⁸

Prevalence and incidence of cervical squamous intraepithelial lesions,^{39, 40} a precursor of cervical cancer, are strongly associated not only with HIV infection, but also with a declining CD4 cell count, a higher plasma HIV RNA level, and presence of human papillomavirus (HPV).^{41, 42} In HIV-infected women, HPV infections are more prevalent and persistent than in women not infected with HIV,⁴³ and HPV-associated disease is more likely to be multicentric, involving the vulva, vagina, and cervix.⁴⁴ Moreover, persistent infections among HIV-infected women are often with viral types associated with HPV-16 or HPV-18, the types most strongly associated with cervical cancer.⁴³ Longitudinal evaluations revealed a higher incidence of invasive cervical cancer in HIV-infected women,⁴⁵ and an incidence of HPV-induced vulvovaginal lesions 16 times greater in HIV-infected women compared with women not infected.⁴⁶ However, reduced progression and increased regression of HPV-related abnormalities have been observed in women treated with highly active antiretroviral therapy (HAART).⁴⁷

Concerns about possibly higher prevalence and severity of lower genital tract infections and menstrual irregularities in HIV-infected women have not been borne out. In the HERS and WIHS cohort studies, women had a low prevalence of infections such as gonorrhea and chlamydia.^{48, 49} The prevalence of clinical bacterial vaginosis was variable with a range of 15% to 33% in both HIV-infected and high-risk uninfected women, and not consistently associated with HIV seropositivity.^{48, 49} Also, although HIV-infected women with pelvic inflammatory disease may be more likely to have adenexal masses than women not infected with HIV, HIV-infected women respond equally well to standard antibiotic treatment.⁵⁰ Overall, HIV does not appear to have a clinically relevant effect on menstruation or other vaginal bleeding.^{51, 52}

Antiretroviral Therapy

Treatment strategies involving HAART are the most effective interventions to date in preventing progression of HIV disease, although additional clinical research involving antiretroviral therapy is needed. Women are increasingly included in trials of antiretroviral agents, and currently account for 17% of participants in Adult AIDS Clinical Trials Group trials enrolling women (J. F. McTigue, written communication, July 2000). Even when proportionally represented, the absolute number of women in trials remains small, and power to detect sex differences in efficacy and adverse effects may be limited, pointing to the need to enroll additional numbers of women in clinical trials, and thus, expand their participation. Further assessment of the effects of antiretroviral therapy in clinical practice is required.

Major declines of 23% overall and 10% among women compared with the previous year in AIDS-related mortality were seen as early

▲
ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

▼
INDEX OF FIGURES AND TABLES

as 1996,⁵³ temporally related to the increased use of combination therapy. In real-world study settings in which participants have access to good HIV clinical care, morbidity and mortality rates have declined dramatically since mid-1995, regardless of sex.⁵⁴

ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

INDEX OF FIGURES AND TABLES

Current treatment guidelines thus recommend antiretroviral management for women and men based on clinical, virologic, and immunologic status, but not sex.²⁹ Although large interindividual variabilities exist, available data have indicated that the pharmacokinetics of antiretrovirals rarely differ by sex alone,⁵⁵ although a better understanding of pharmacokinetics overall is needed. Hormonal factors and pregnancy may affect the choice of antiretrovirals for women. Specifically, nelfinavir, ritonavir, amprenavir, and efavirenz may decrease the efficacy of hormonal contraceptives by altering hormonal levels 18% to 47%, necessitating use of alternative or additional methods of contraception.²⁹ And, while data on pharmacokinetic changes and adverse effects of antiretrovirals in pregnancy are limited, efavirenz is contraindicated in the first trimester of pregnancy due to possible teratogenic effects, and indinavir should be avoided late in pregnancy due to theoretical concerns regarding hyperbilirubinemia and nephrolithiasis.²⁹ Otherwise, guidelines for optimal antiretroviral therapy in pregnant women are similar to those for nonpregnant adults, and pregnancy itself is an indication for (possibly limited) antiretroviral treatment to prevent vertical HIV transmission.²⁹

Biological potential for sex-related differences in adverse effects exists, due to weight, metabolism, hormones, and other factors. Weight-related differences are of particular concern as women generally have a lower lean body weight than men.⁵⁶ However, while women may be more likely than men to report adverse effects,⁵⁷ these reports are higher among women receiving either study drug or placebo. For example, in a trial in which women were more likely than men to report adverse effects from ritonavir, this effect disappeared after adjusting for the placebo group.⁵⁷

Even more difficult to differentiate are sex influences on syndromic toxic effects thought to be related to antiretroviral therapies. Whether hyperglycemia, lactic acidosis, and lipodystrophy (elevated lipids and physical fat maldistribution) are the effects of specific antiretroviral medications, duration of HIV infection, patient age, or a combination of factors is still not clear.⁵⁸ Women receiving antiretroviral therapy may be more likely than men to have hyperglycemia.⁵⁹ They may also be more prone to lactic acidosis. Of 60 cases of lactic acidosis among persons receiving combination antiretroviral therapy reported to the Food and Drug Administration through June 1998, 83% occurred in women.⁶⁰ And while elevation of lipid levels after initiation of antiretroviral therapy in women has been reported,⁶¹ it may occur less frequently in women than men.⁵⁹ Signs of fat maldistribution including increased breast and abdominal girth may be common among women taking protease inhibitor drugs,⁶² but are also found in those not taking protease inhibitors.⁶³ There needs to be better understanding of the causes of these syndromic toxic effects and their ameliorating factors before recommendations in this regard can be made for HIV-infected women.

Use of and Adherence to Antiretroviral Therapy

Use of antiretroviral therapy by women has been improving, for example, by 1998, 80% of women with AIDS in HERS and WIHS had received some sort of antiretroviral therapy.⁶⁴ However, women may still be less likely than men to receive HAART,⁶⁵ perhaps because they are often black, less educated, or injection drug users

ABSTRACT

INTRODUCTION

— factors associated with lower likelihood of using antiretroviral medications.^{64, 65} Beliefs about therapy may also limit use by women and men, with non-HAART users more likely to believe that HIV can be fought off without medication and less likely to believe that antiretroviral medications prolong survival.⁶⁵

METHODS**RESULTS****COMMENT****AUTHOR/ARTICLE INFORMATION****REFERENCES****INDEX OF FIGURES AND TABLES**

Sex alone does not predict adherence to HAART.^{66, 67} Like men, only about three quarters of women receiving therapy report taking medications as or almost as directed.^{64, 68} Common reasons for nonadherence, in women and men, are forgetting to take pills and drug adverse effects,⁶⁴ but many other reasons, such as not understanding how to take medications, forgetting refills, depressed mood, life-stress, anxiety, and pain,^{64, 66-68} also pertain and may vary by sex.⁶⁶

Use of Health Services

Use of regular health services, especially ongoing primary care, will facilitate the appropriate management of HIV. While use of regular health services has been improving, the gap between HIV-infected women and men remains.⁶⁹ Women infected with HIV report worse physical functioning than men at similar stages of disease,⁷⁰ are more likely to use emergency department services for outpatient care,⁶⁹ and are more often underinsured.⁷¹ When access is less of a problem, such as in prison or when continuously enrolled in Medicaid, HIV-infected women tend to use more health services than similar HIV-infected men or women not infected but who are at risk for HIV.⁷²⁻⁷⁴

Barriers to use of health services for women include lack of insurance, current injection drug use, and difficulty remembering appointments.⁷⁵ Competing subsistence needs are also important for both women and men. For example, going without care because of needing money for food, clothing, or housing, or postponing care because of lack of transportation have all been associated with using the emergency department for outpatient care and reporting low overall access to care.⁷⁶ Unmet needs for basic necessities such as child care remain high among HIV-infected persons with dependents and may disproportionately affect women.⁷⁷ Supplementing unmet competing needs may be necessary to maximize use of available health services.

Depression and Psychological Distress

Early reports of high levels of depressive symptoms, possibly associated with CD4 cell count decline, among HIV-infected men⁷⁸ stimulated investigation of depression among women. In general, women have higher rates of depression than men.⁷⁹ Among both HIV-infected women and women not infected but who are at risk for HIV, rates of significant depressive symptoms and adverse life events exceed 60%.⁸⁰ Many activities that put a woman at risk for HIV, such as drug use and sex trading, are associated with high rates of psychological distress, regardless of the woman's HIV infection status.^{81, 82} HIV infection may be a less immediate and pressing problem than those other problems attendant to depression, drug use, and sex trading. Moreover, the impact of depression on adherence to and continuation of therapy⁶⁴ may adversely affect the course of disease and mortality rates. Thus, identification and treatment of psychological disorders in women with and at risk for HIV infection require attention.

**ABSTRACT****INTRODUCTION****METHODS****RESULTS****COMMENT****AUTHOR/ARTICLE INFORMATION****REFERENCES****Social Challenges**

Activities that put women at risk for HIV, such as injection drug and

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crack cocaine use and high-risk sex behavior, also put them at risk for violence, family problems, and inadequate social support. Women in both the HERS and WIHS cohorts were at high risk for violence (including rape) regardless of HIV status, with approximately 66% reporting violence during their adult lifetime and 30% to 40% reporting childhood sex abuse.^{83, 84} Although HIV-infected women in the HERS cohort who had disclosed HIV test results to a partner did not have a higher rate of recent violence,⁸³ assessment of an individual's needs for protection and support surrounding disclosure is still important.

Women with and at risk for HIV often lack adequate familial or social support. In the HERS cohort, one third of women had a family member with HIV/AIDS, most often a sibling.⁸⁵ This may strain familial resources and place additional caregiver responsibilities on women. Within illicit drug distribution networks, women often have little economic or social power, rely on exchange of sex for drugs or money, and have few women friends and strained familial relationships.⁸⁶ Women with or at risk for HIV also report legal needs relating to housing, debt, and child care.⁸⁷ Women's burdens related to their roles in society and the effects of poverty, racism, and drug culture serve to create demands that can extend beyond that of HIV infection.

Risk Behaviors

Reducing risk behaviors among HIV-infected persons is important to limit transmission of HIV to uninfected persons and to limit acquisition of potentially resistant variants of HIV by infected persons. In HERS and WIHS, HIV-infected women were more than twice as likely as uninfected women to report consistent condom use,^{88, 89} particularly with uninfected partners.⁸⁹ Crack cocaine and injection drug use are strong predictors of inconsistent condom use for both HIV-infected and uninfected women.⁸⁹ A partner's desire not to use a condom is a frequently reported reason for inconsistent use, even among HIV-infected women with HIV-uninfected partners.⁸⁹

▲

ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

▼

INDEX OF FIGURES AND TABLES

In general, it appears that many women are concerned about preventing infection of others. Compared with uninfected women, HIV-infected women in both HERS and WIHS report less sexual activity and may be more likely to have only 1 sex partner,^{88, 90} primarily because of fear of infecting a partner.⁹⁰ Women infected with HIV in HERS were more likely to want to avoid pregnancy and to use contraceptives because of beliefs that perinatal HIV transmission is likely and that pregnancy for HIV-infected women is unacceptable (G. Millet, unpublished data, 2000). However, decision making regarding pregnancy may change now that interventions such as antiretroviral therapy in conjunction with cesarean delivery have decreased, although not eliminated, perinatal transmission in the United States.¹¹ Pregnancy rates (fertility) are lower in HIV-infected women, but it is not clear if this is due to the HIV virus itself or other factors such as contraceptive use (reproductive choices), and previous sexually transmitted infections.⁹¹ Continued educational efforts directed at women with HIV infection and their partners are important.

COMMENT

Over the past decade, our scientific knowledge regarding HIV

infection in women has increased greatly. Women with HIV infection appear to have a natural history of infection similar to that of men, including range of HIV-associated illnesses, and rates of progression of disease. Knowledge has evolved regarding the risks and manifestations of sex-specific diseases, and women can benefit greatly from appropriate treatment with HAART. The effects of drug use, poverty, and competing needs of women with HIV infection have been shown to interfere with preventive behaviors and use of health services, including antiretroviral therapy. Thus, as the third decade of the HIV epidemic begins, continued research on HIV basic science and clinical research leading to advances in care is needed; however, emphasis should also be placed on applying existing knowledge about HIV prevention and treatment in women by enhancing use of available health services and including greater use of antiretroviral therapy options, treating depression and drug use, facilitating educational efforts, and providing social support to reduce competing needs that prevent women from taking control of HIV prevention and treatment.

Author/Article Information

ABSTRACT
INTRODUCTION
METHODS
RESULTS
COMMENT
AUTHOR/ARTICLE INFORMATION
REFERENCES
INDEX OF FIGURES AND TABLES

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REFERENCES

ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

INDEX OF FIGURES AND TABLES

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ABSTRACT

INTRODUCTION 2001.

METHODS 10.
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AUTHOR/ARTICLE INFORMATION 11.
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INDEX OF FIGURES AND TABLES 13.
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ABSTRACT 18.
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INTRODUCTION 19.
METHODS
RESULTS
COMMENT
AUTHOR/ARTICLE INFORMATION
REFERENCES

INDEX OF
FIGURES AND
TABLES

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ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE
INFORMATION

REFERENCES

INDEX OF
FIGURES AND
TABLES

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INDEX OF FIGURES AND TABLES
▼

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ABSTRACT
INTRODUCTION
METHODS
RESULTS
COMMENT
AUTHOR/ARTICLE INFORMATION
REFERENCES

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INDEX OF
FIGURES AND
TABLES

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INTRODUCTION

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COMMENT

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INFORMATION

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INDEX OF
FIGURES AND
TABLES

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ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

**AUTHOR/ARTICLE
INFORMATION**

REFERENCES

**INDEX OF
FIGURES AND
TABLES**

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▲
ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

INDEX OF FIGURES AND TABLES

▼

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▲
ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

INDEX OF FIGURES AND TABLES

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ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE INFORMATION

REFERENCES

INDEX OF
FIGURES AND
TABLES

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ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE
INFORMATION

REFERENCES

INDEX OF
FIGURES AND
TABLES

ABSTRACT

INTRODUCTION

METHODS

RESULTS

COMMENT

AUTHOR/ARTICLE
INFORMATION

REFERENCES

INDEX OF
FIGURES AND
TABLES

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